THERAPEUTIC USES OF NON-STEROIDAL ANTI-INFLAMMATORY DRUGS IN DENTISTRY

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ABSTRACT: The non-steroidal anti-inflammatory drugs (NSAIDs) are among the most widely used classes of drugs for the management of acute and chronic pain in dentistry. Their therapeutic efficacy and toxicity are well-documented and provide evidence that NSAIDs generally provide an acceptable therapeutic ratio of pain relief with fewer adverse effects than the opioid-mild analgesic combination drugs that they have largely replaced for most dental applications. The great many studies done with the oral surgery model of acute pain indicate that a single dose of an NSAID is more effective than combinations of aspirin or acetaminophen plus an opioid, with fewer side-effects, thus making it preferable for ambulatory patients. The combination of an NSAID with an opioid generally results in marginal analgesic activity but with an increased incidence of side-effects, which limits its use to patients in whom the NSAID alone results in inadequate analgesia. The selective COX-2 inhibitors hold promise for clinical efficacy with less toxicity from chronic administration and may prove advantageous for the relief of chronic orofacial pain. The use of repeated doses of NSAIDs for chronic orofacial pain should be re-evaluated in light of a lack of documented efficacy and the potential for serious gastrointestinal and renal toxicity with repeated dosing.

Key words. NSAIDs, acute pain, chronic pain, edema, preventive analgesia.

Introduction

The management of pain and inflammation in dentistry has several unique features. Pain not only signals tissue injury, but it also acts as an impediment to most dental procedures, delays the resumption of normal activities following dental surgical procedures, and lessens the likelihood of patients seeking dental procedures in the future. While pain during therapy is usually adequately controlled by local anesthesia, post-operative pain control is often inadequate, because of either insufficient relief of pain or unacceptable side-effects. Side-effects such as drowsiness, nausea, and vomiting from opioids occur with greater frequency in ambulatory dental patients than in non-ambulatory hospitalized patients. In addition, inadequate pain control during the immediate post-operative period may contribute to the development of hyperalgesia (Gordon et al., 1997a), leading to greater pain at later time points during recovery. Pain associated with dentistry is also known to contribute to apprehension about future dental care, such that patients frequently report themselves as very nervous or terrified at the prospects of dental care (Gordon and Dionne, 1997). These considerations indicate that optimal analgesic therapy for ambulatory dental patients should be efficacious, with a minimum incidence of side-effects, and, ideally, should lessen the prospects for pain associated with future dental therapy.

Non-steroidal anti-inflammatory drugs (NSAIDs) are the mainstay of therapy for the management of acute dental pain. They have also been evaluated for chronic orofacial pain, as an adjunct to the treatment of periodontal disease, to minimize edema following surgical procedures, and for endodontic pain. The toxicity associated with chronic NSAID administration is well-documented and reportedly results in greater than 100,000 hospitalizations per year, suggesting that the benefit-to-risk relationship should be carefully weighed for each therapeutic indication. The new generation of selective cyclo-oxygenase (COX)-2 inhibitors holds promise that the therapeutic effects of traditional NSAIDs can be achieved without the toxic renal and GI effects, but these have not been adequately studied for dental indications or in large numbers of subjects. The use of NSAIDs for dentistry is critically evaluated in this review within the context of their documented toxic effects, and rational therapeutic uses will be suggested, as will applications that should be re-considered or, at the least, re-evaluated in future studies.

Knowledge of the clinical pharmacology of NSAIDs is based in large part on studies performed in the oral surgery model of acute pain (Cooper and Beaver, 1976). Impacted third molars are surgically removed in a clinical trial that facilitates comparison of a drug under study with a placebo, a standard drug, or both, under conditions which attempt to control for factors that normally confound assessment of analgesic activity in humans. Ibuprofen, the prototype of the NSAID class, has demonstrated analgesic activity over a dose range from 200 to 800 mg, with a duration of activity from 4 to 6 hrs (Cooper, 1984). When given prior to pain onset, it suppresses the onset of pain and lessens its severity (Dionne and Cooper, 1978; Dionne et al., 1983). Ibuprofen suppresses swelling over the initial two- to three-day post-operative course, when edema formation associated with the inflammatory process is most prominent. Interactions with the release of β-endorphin have been demonstrated both intra-operatively during surgical stress and during post-operative pain, suggesting that NSAIDs can modify the neurohumoral responses to pain (Dionne and McCullagh, 1998; Troullos et al., 1997). The wealth of data from clinical trials using NSAIDs supports these generalizations and makes NSAIDs among the most well-studied drug classes for acute inflammatory pain in ambulatory patients.

(II) Analgesia

(A) Ibuprofen

Ibuprofen is the prototype of the NSAID class of analgesics and was first introduced into clinical practice in the US in 1974. It is particularly useful for conditions in which aspirin or acetaminophen does not result in adequate pain relief or where the use of opioid-containing combinations would likely result in central nervous system or gastrointestinal side-effects. It is widely used for acute and chronic orofacial pain by prescription in doses of 600 to 800 mg, and as a non-prescription analgesic in 200- to 400-mg doses (all mg doses are for a single administered dose unless otherwise stated).

Ibuprofen in a dose of 400 mg has been found superior to 650 mg of aspirin, 600 to 1000 mg acetaminophen, combinations of aspirin and acetaminophen plus 60 mg of codeine (Cooper *et al.*, 1977; Jain *et al.*, 1986; Forbes *et al.*, 1984), as well as dextropropoxyphene 65 mg (Winter *et al.*, 1978). A single dose of ibuprofen 400 mg or administration of multiple doses up to 5 days post-operatively was superior to 30 mg of dihydrocodeine in the oral surgery model (Frame *et al.*, 1989; McQuay *et al.*, 1993). Administration of doses greater than 400 mg is not likely to result in greater peak relief, but increased drug blood levels may prolong the duration of effect (Laska *et al.*, 1986).

Ibuprofen appears comparable with other NSAIDs when evaluated in the oral surgery model. Ibuprofen 400 mg produces analgesia similar to that produced by 100 mg of meclofenamate sodium but with a lower incidence of stomach pain and diarrhea (Hersh *et al.*, 1993). Ibuprofen 200 mg results in onset and peak analgesia similar to those of, but a duration shorter than, 220 mg of naproxen sodium when evaluated up to 12 hrs following a single dose (Kiersch *et al.*, 1993). This reported shorter duration has little clinical significance, since the normal dosing interval for low-dose ibuprofen is every 4 to 6 hrs. The 400-mg dose of ibuprofen was also similar to a suspension formulation of diclofenac in a study with sample sizes (N = 80-83) sufficiently large to detect differences (Bakshi *et al.*, 1994). No advantage could be demonstrated between tablets and soluble formulations of 200-mg, 400-mg, and 600-mg ibuprofen evaluated up to 6 hrs post-operatively (Seymour *et al.*, 1996). No dose-related difference could be demonstrated in this study between the 400-mg and 600-mg dose of either formulation, leading the authors to conclude that there is little advantage in increasing the dose to 600 mg.

Ibuprofen has also been evaluated for dental pain other than that from oral surgery. Periodontal surgery involves elevation of a surgical flap, often of considerable size, with osseous reshaping and implantation of materials to replace bone lost to the disease process, and can last 2 to 3 hrs. Ibuprofen in doses of 200 and 400 mg was demonstrated to be superior to placebo in a single dose over a six-hour observation period following periodontal surgery, with a low incidence of adverse effects (Vogel and Gross, 1984). Ibuprofen 600 mg given either immediately prior to periodontal surgery or following the procedure demonstrated a suppression of pain intensity in comparison with placebo over the first 8 hrs post-operatively (Vogel *et al.*, 1992). Dosing after surgery appeared to result in greater pain suppression over the last 4 hrs of the observation period, consistent with the expected six-hour duration of ibuprofen 600 mg and the duration of the intervening surgery (2 to 3 hours).

Patients undergoing orthodontic tooth movement can experience various degrees of discomfort, especially over the first few days following placement or adjustment of orthodontic devices. Administration of a single dose of ibuprofen 400 mg in comparison with aspirin 650 mg and placebo demonstrated that both active drugs suppressed pain in comparison with placebo up to 7 days following placement of orthodontic devices (Ngan *et al.*, 1994). Ibuprofen was superior to aspirin at most time points over the first two days, suggesting that it is suppressing the inflammatory response normally seen following orthodontic adjustments.

A less-well-characterized indication for the use of NSAIDs is in the management of endodontic pain. Pain from pulpal or periapical tissues is a major reason that patients seek urgent dental care. While the management of pain with endodontic treatment is primarily aimed at removing the necrotic or inflamed tissue, a variety of pro-inflammatory mediators is released and may contribute to post-operative discomfort. Mechanical debridement and the use of canal medicaments also contribute to periapical inflammation that persists beyond the duration of local anesthesia. While the results of analgesic studies conducted with the oral surgery model could be extrapolated to pain of endodontic origin, a few studies have directly addressed the use of NSAIDs for endodontic procedures.

Ibuprofen was compared with a wide variety of drug treatments following an endodontic procedure (root canal obturation), but none of the 9 drug groups could be differentiated from placebo (Torabinejad *et al.*, 1994a). This may reflect a lack of assay sensitivity for this model, since only 4% of the patient sample (N = 411) developed moderate or severe pain, the remainder reporting no pain or mild pain. Endodontic pain has previously been demonstrated as being sensitive to the effects of NSAIDs (Flath *et al.*, 1987), but only when subjects who are symptomatic prior to the procedure are included in the analyses. Most patients who are pain-free prior to an endodontic procedure report little pain post-operatively (Torabinejad *et al.*, 1994b).

(B) Naproxen

Naproxen is also a propionic acid derivative but is longer-acting than ibuprofen. It is available in two formulations, with the sodium salt being more rapidly absorbed than naproxen. The different formulations should not be used concomitantly, because they both circulate in plasma as the naproxen anion, and the resultant additive plasma concentration increases the possibility of dose-related adverse effects. An initial loading dose of 500 to 550 mg is used to reach therapeutic levels more rapidly, with subsequent doses of 250 to 275 mg given at six- to eight-hour levels. A single 550-mg dose of naproxen sodium has greater analgesic activity than 650 mg of aspirin, with a lower incidence of side-effects (Sevelius *et al.*, 1980). A repeat-dose comparison of 500 mg naproxen twice a day with aspirin 650 mg for three days following oral surgery also demonstrated greater efficacy and fewer side-effects for naproxen (Sindet-Pedersen *et al.*, 1986). For dental pain, 550 mg of naproxen was found to be more efficacious than 325 mg of aspirin plus 30 mg codeine (Reudy, 1973). This combination, however, is half the normal therapeutic dose of aspirin and codeine when used in combination—that is, 650 mg acetaminophen plus 60 mg codeine. Both pre-operative naproxen and naproxen administered 30 min following oral surgery suppress pain over the first 8 hrs post-operatively (Sisk and Grover, 1990). Lack of a parallel placebo group, however, makes it difficult to determine if this represents an equal suppression of post-operative pain by

either treatment regimen or lack of assay sensitivity.

Over-the-counter (OTC) naproxen sodium was introduced in 1994 in a formulation containing 220 mg with a recommended dose of 1 or 2 tablets twice daily. A review of 48 randomized double-blind clinical studies (25 in the dental pain model) indicates no overall difference in the rate of adverse events seen for naproxen sodium in comparison with placebo, ibuprofen, or acetaminophen (DeArmond *et al.*, 1995). Analysis of these data suggests that OTC naproxen is well-tolerated even when administered in the absence of professional supervision.

(C) Ketoprofen

Ketoprofen is chemically related to other propionic acid derivatives with analgesic and antipyretic properties. Like other NSAIDs, it acts peripherally *via* inhibition of prostaglandin and leukotriene synthesis but is also thought to act centrally as well (Willer *et al.*, 1989). Ketoprofen is effective as an analgesic for the relief of mild to moderate pain in doses ranging from 25 to 150 mg, with greater efficacy than 650 mg aspirin (Cooper *et al.*, 1984) or codeine 90 mg (Mehlisch *et al.*,1984). Ketoprofen 25 mg is therapeutically equivalent to 400 mg of ibuprofen (Fig. 1) in the oral surgery model (Cooper *et al.*, 1988a).

Recently, this drug has been evaluated for its efficacy following local administration at the site of injury as a strategy for decreasing systemic exposure to NSAIDs. A gel formulation was placed directly into the extraction site 1 hr following oral surgery, and subsequently pain intensity was evaluated for 6 hrs. Significantly less pain was seen following peripheral administration of both 10 and 30 mg ketoprofen in comparison with the placebo. Peripheral administration of the 10-mg dose also resulted in greater analgesia than oral administration of the same dose formulation or the placebo (Dionne *et al.*, 1999). Analysis of these data indicates that administration of an NSAID to a peripheral site of tissue injury results in greater analgesia than oral administration and suggests the potential for less drug toxicity through lower circulating drug levels.

(D) Flurbiprofen

Flubiprofen is a phenylalkanoic acid derivative, structurally related to ibuprofen, ketoprofen, and naproxen, with anti-inflammatory, analgesic, and antipyretic activity in man and animal models of pain and inflammation. It has been evaluated extensively for the management of acute pain and management of the discomfort associated with rheumatoid arthritis and osteoarthritis. Post-operative administration of flurbiprofen over the dose range of 50 to 150 mg results in a linear increase in analgesia in the oral surgery model, with all doses yielding results superior to those achieved with aspirin 600 mg (Cooper *et al.*, 1988b). Flubiprofen at doses of 50 and 100 mg is also superior to acetaminophen 650 mg and acetaminophen 650 plus codeine 60 mg for post-operative dental pain (Dionne *et al.*, 1994). A lower dose of flurbiprofen (25 mg) has also been demonstrated to produce greater pain relief than the standard 650-mg dose of aspirin (Mardirossian and Cooper, 1985).

Administration of flurbiprofen prior to oral surgery suppresses the onset and intensity of post-operative pain in comparison with placebo, acetaminophen, acetaminophen plus oxycodone (Dionne, 1986), or the combination of aspirin 375 mg, codeine 30 mg, and caffeine 30 mg (Dupuis *et al.*, 1988). Post-operative edema at 48 and 72 hrs is also reduced by the administration of flurbiprofen prior to oral surgery (Troullos *et al.*, 1990).

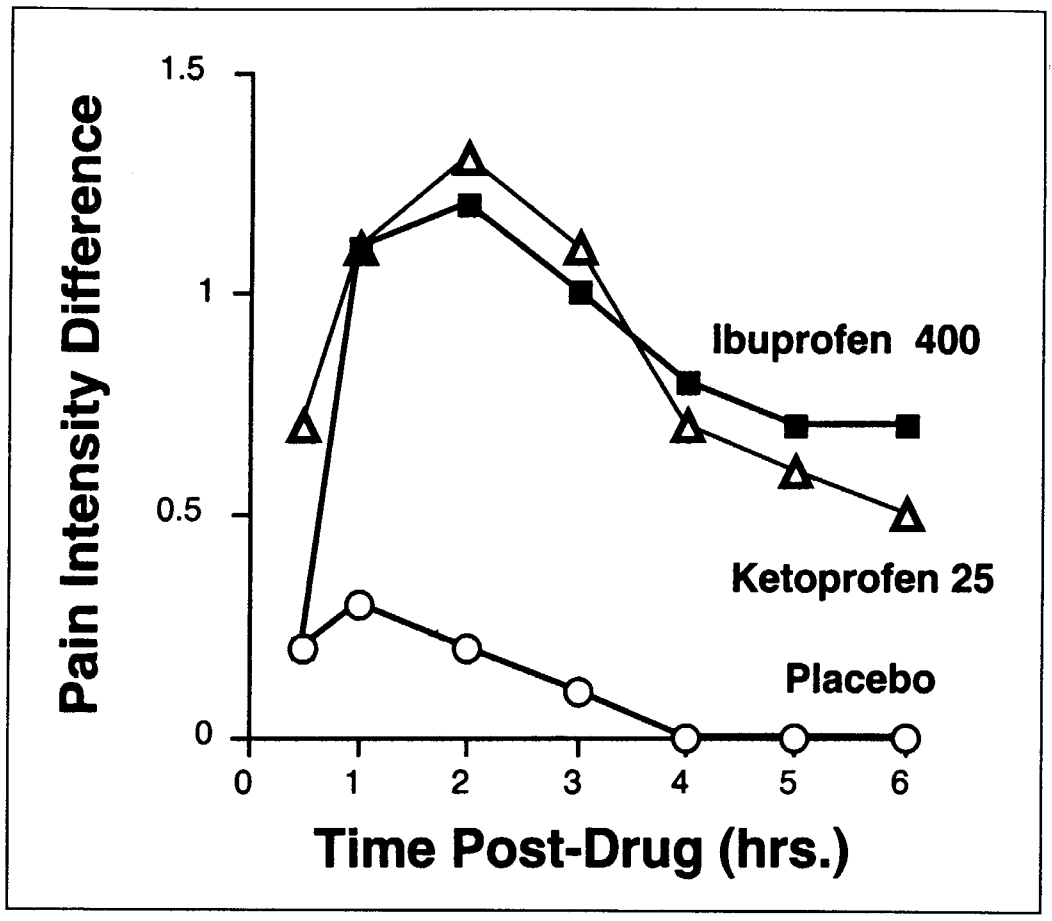

Figure 1. Analgesic equivalency of ibuprofen and ketoprofen at usual analgesic doses, demonstrating that marketed doses of different NSAIDs result in similar levels of analgesia. Adapted from Cooper SA, 1997 (unpublished observations).

When flurbiprofen pre-treatment is combined with the use of a long-acting local anesthetic such as etidocaine, pain in the immediate post-operative period is dramatically reduced (Dionne *et al.*, 1984; Dionne, 1986).

Pre-operatively administered flurbiprofen (100 mg) was evaluated for suppressing pain after pulpectomy in 60 asymptomatic and symptomatic patients. At 7 and 24 hrs after the first dose of medication, the symptomatic patients reported statistically less pain than the placebo group (Flath *et al.*, 1987). Subjects who were asymptomatic patients prior to pulpectomy did not report appreciable pain after the local anesthetic effects dissipated, making it difficult to differentiate between treatment groups. While limited by the moderate sample size in the report by Flath *et al.*, these data support the use of NSAID pre-treatment before endodontic procedures to suppress post-operative pain.

Although approved by the Food and Drug Administration (FDA) for the management of rheumatoid arthritis and osteoarthritis, flurbiprofen has never been formally approved as an analgesic. The analgesic superiority demonstrated for flurbiprofen in controlled clinical trials and the millions of doses administered safely to patients with arthritis support the use of flurbiprofen for acute dental pain.

(E) Etodolac

Etodolac is indicated as an analgesic based on its efficacy in the oral surgery model and a more favorable profile of GI safety. In a dose-range study (50, 100, and 200 mg), the analgesic effect of the 200-mg etodolac dose was significantly greater than that of placebo for virtually all measures of analgesia. While numerically superior to aspirin, the 200-mg dose of etodolac was statistically superior only on the patient's global evaluation of analgesic activity, while resulting in a duration that was approximately twice as long. All etodolac doses were equally well-tolerated in comparison with aspirin (Nelson and Bergman, 1985). A study comparing etodolac 300 mg with the combination of acetaminophen/hydrocodone for

post-operative pain following periodontal surgery found the drugs to be equivalent over the first 8 hrs (Tucker *et al.*, 1996). Etodolac administered prior to surgery, however, suppressed the time to the first post-operative dose of medication, supporting the value of preventive analgesic treatment in this model. Analysis of these data suggests therapeutic equivalence for etodolac to other commonly used analgesics.

Etodolac is reported to be 10-fold more selective for COX-2 in comparison with its effect on COX-1. This sparing of COX-1 activity gives rise to greater gastric tolerance, and this beneficial effect has been demonstrated in many studies (Dvornik, 1997). Analysis of these limited data in the oral surgery model suggests that etodolac is useful as an analgesic for dental indications. It has a prolonged duration of action and favorable GI safety with repeated administration.

(F) Ketorolac

Ketorolac is the first NSAID approved for intramuscular administration for the short-term management of moderate to severe pain (Micaela and Brogden, 1990). It has also been approved for intravenous administration and has been used successfully even in selected pediatric cases (Houck *et al.*, 1996). It has been compared with intramuscular (IM) meperidine and IM morphine in several analgesic models and appears to have comparable onset and analgesic efficacy as well as being longer-acting. Ketorolac 30 mg provides pain relief comparable with that from meperidine 100 mg (Stanski *et al.*, 1990) or morphine 10 mg (Spindler *et al.*, 1990). Ketorolac causes less drowsiness, nausea, and vomiting than morphine 12 mg (O'Hara *et al.*, 1987). The ability of injectable ketorolac to overcome the normally slow onset of NSAIDs when given orally, combined with analgesic efficacy comparable with that of parenteral opioids and reduced side-effects (Fig. 2), suggests that it can be used preferentially for the management of pain not adequately controlled by other NSAIDs or opioid combinations. This route of administration, however, limits its use to ambulatory patients for the initial dose prior to discharge.

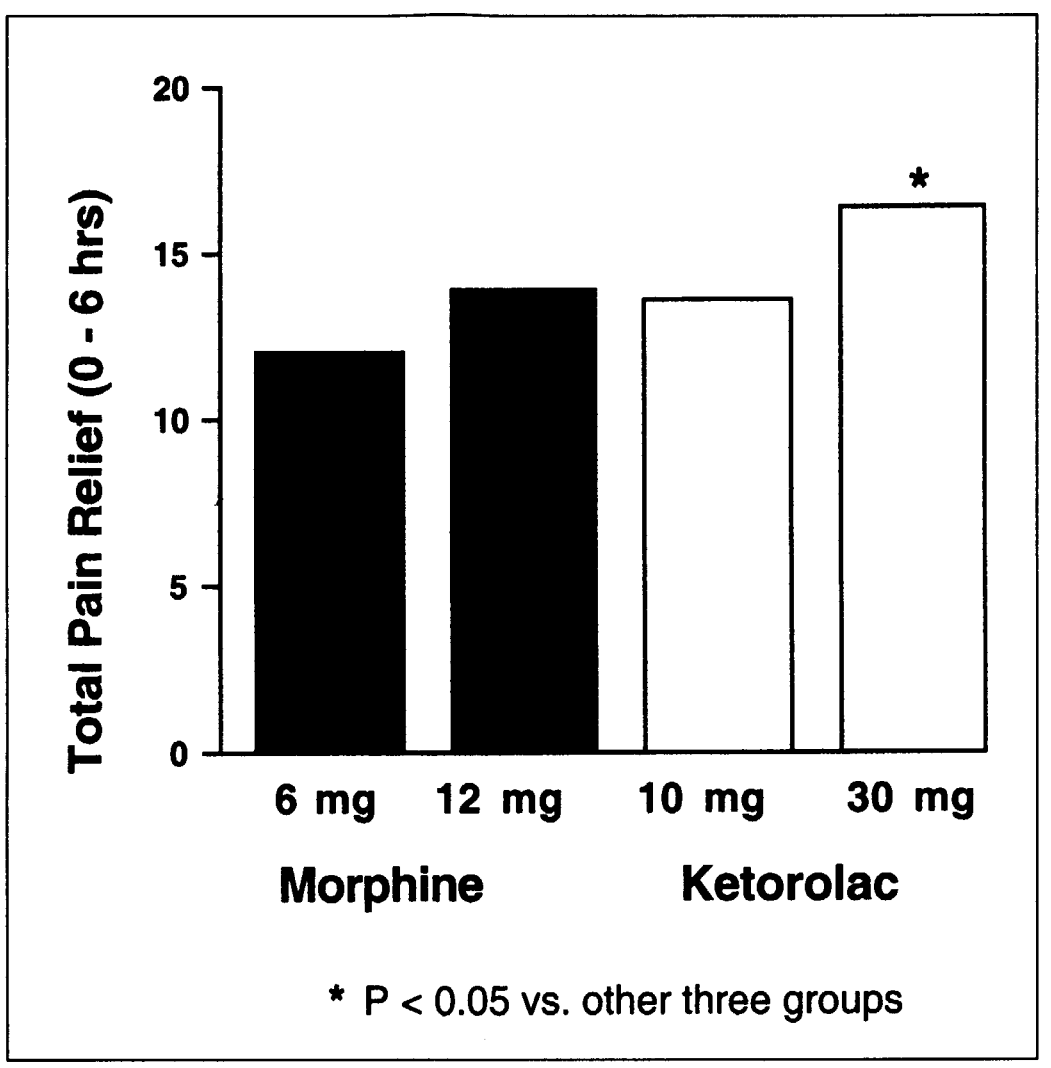

Figure 2. Demonstration of analgesic efficacy for the NSAID ketorolac approximately equivalent to that of therapeutic doses of morphine (upper panel) but with a lower incidence of side-effects (lower panel).

An open-label comparison of orally administered ketorolac 10 mg with the same dose injected into the buccal vestibule of an endodontically treated tooth failed to differentiate between the two formulations; the lack of a placebo group, however, limits interpretation of therapeutic equivalency (Battrum and Gutmann, 1996). Another study also evaluated the local administration of injectable ketorolac in 52 endodontic emergency patients after pulpotomy. Maxillary or mandibular infiltration of 30 mg ketorolac produced significant analgesic effects (Penniston and Hargreaves, 1996). An interesting observation was a demonstration of analgesic effects for the mandibular infiltration, contrary to the poor efficacy usually reported for local anesthetic infiltration in the mandible. It also appears that the presence of inflammation did not hinder the analgesic effect of ketorolac infiltration, nor did the injection of ketorolac result in any tissue irritation. Analysis of these data, although from only one study, suggests that the intra-oral injection of ketorolac may prove to be a useful adjunct to the management of endodontic pain, especially in cases where local anesthetic administration is ineffective due to the presence of inflammation or at a mandibular site of injection.

Ketorolac is also available for oral administration at a dose of 10 mg every 4 to 6 hrs; the total daily dose should not exceed 40 mg. A labeling change by the FDA recommends that oral ketorolac be used only when the injectable form has first been administered. For oral surgery pain, a single dose of 10 mg of oral ketorolac is superior to acetaminophen 600 mg, and acetaminophen 600 mg plus codeine 60, but therapeutically equivalent to 400 mg ibuprofen (Forbes *et al.*, 1990). Oral administration of ketorolac results in faster absorption in comparison with intramuscular administration (Jung *et al.*, 1989). The lower recommended oral dose (10 mg) compared with the parenteral dose (30 to 60 mg), however, results in much lower peak blood levels and less analgesia than parenteral ketorolac.

(G) Meclofenamate Sodium

Meclofenamate sodium is an NSAID with analgesic, anti-inflammatory, and antipyretic activity. It acts simultaneously to inhibit both the cyclo-oxygenase and lipoxygenase pathways, resulting in reduced formation of prostaglandins and leukocytes (Boctor *et al.*, 1985; Rees *et al.*, 1987). In the oral surgery model, meclofenamic acid results in analgesia superior to that of aspirin (Markowitz *et al.*, 1985; Rowe *et al.*, 1985), acetaminophen (Cooper *et al.*, 1988c), and acetaminophen plus codeine (Cooper *et al.*, 1988c). Unlike other NSAIDs, it does not significantly interfere with platelet aggregation or prolong bleeding time (Meclomen product information; **Physicians' Desk Reference**, 1993).

(H) Piroxicam

Piroxicam is an oxicam NSAID; its plasma half-life has been estimated at 45 hrs, allowing for once-daily dosing, with peak plasma concentration occurring 2 to 4 hrs after oral administration (Insel, 1996). Piroxicam, in single doses of 20 to 40 mg, has been shown to produce analgesia approximately equivalent to the effects of aspirin 648 mg but with a longer duration

of action (Desjardins, 1988). Another study, involving 50 patients, used piroxicam (40 mg) pre-operatively before third molar surgery under general anesthesia. A significant number of those patients did not require opioid analgesia after the operation and also required fewer doses of acetaminophen in the first 24 hrs after recovery from anesthesia (Hutchinson *et al.*, 1990). Analysis of these limited data suggests that piroxicam has less efficacy than other NSAIDs but a longer duration of action. This does not necessarily represent a therapeutic advantage, since patients will often re-medicate prior to the recommended dosing interval if analgesia is inadequate, introducing the possiblity of cumulative gastrointestinal damage (Henry *et al.*, 1998).

(I) Diflunisal

Diflunisal is a salicylic acid derivative [5-(2,4-diflurophenyl) salicylic acid] that is more effective than aspirin but with fewer gastrointestinal and hematologic adverse effects. Evaluation in the oral surgery model demonstrates that diflunisal has greater peak analgesia than aspirin 650 as well as a duration of effect up to 12 hrs, making a twice-daily dosing regimen possible (Forbes *et al.*, 1982). In another oral surgery study (N = 15), mean bleeding time was increased by 53% for the group, but in no patient did the increase exceed the upper limit of normal bleeding time (Chapman and Macleod, 1987). There was no increased tendency for intra-operative or post-operative bleeding. These studies indicate that diflunisal is an alternative to aspirin and other NSAIDs in situations where prolonged duration of action presents a therapeutic benefit.

(III) Preventive Analgesia

Most studies in which an NSAID is administered orally after pain onset demonstrate an onset of activity within 30 min and peak analgesic activity at 2 to 3 hrs post-drug administration. An early attempt to overcome this two- to three-hour delay in peak ibuprofen analgesic activity in the post-operative period involved administration of the drug prior to oral surgery. This allows sufficient time for drug absorption during the surgical procedure and the one- to two-hour duration of standard local anesthetics post-operatively. Pre-operative administration of 400 mg ibuprofen was demonstrated to increase the time to the first post-operative dose of analgesic by approximately 2 hrs in comparison with placebo pre-treatment (Dionne and Cooper, 1978). A subsequent study demonstrated that pre-operative administration of 800 mg ibuprofen significantly lowered pain intensity over the first 3 hrs post-operatively when the residual effects of the local anesthetic had dissipated (Dionne *et al.*, 1983). Administration of a second dose of ibuprofen 4 hrs after the initial dose extended this preventive analgesic effect and resulted in less pain than experienced with placebo, acetaminophen (given both pre- and post-operatively), or acetaminophen plus 60 mg codeine (administered post-operatively). The ability to suppress the onset and lower the intensity of post-operative pain up to 8 hrs is replicable (Hill *et al.*, 1987; Troullos *et al.*, 1990; Berthold and Dionne, 1993) and extends to the use of other NSAIDs such as flurbiprofen (Dionne, 1986).

Comparison of ibuprofen administration prior to periodontal surgery with administration immediately following surgery demonstrated that both groups experienced a significant delay in pain onset in comparison with placebo (Vogel *et al.*, 1992). Also, a similar study with naproxen in the oral

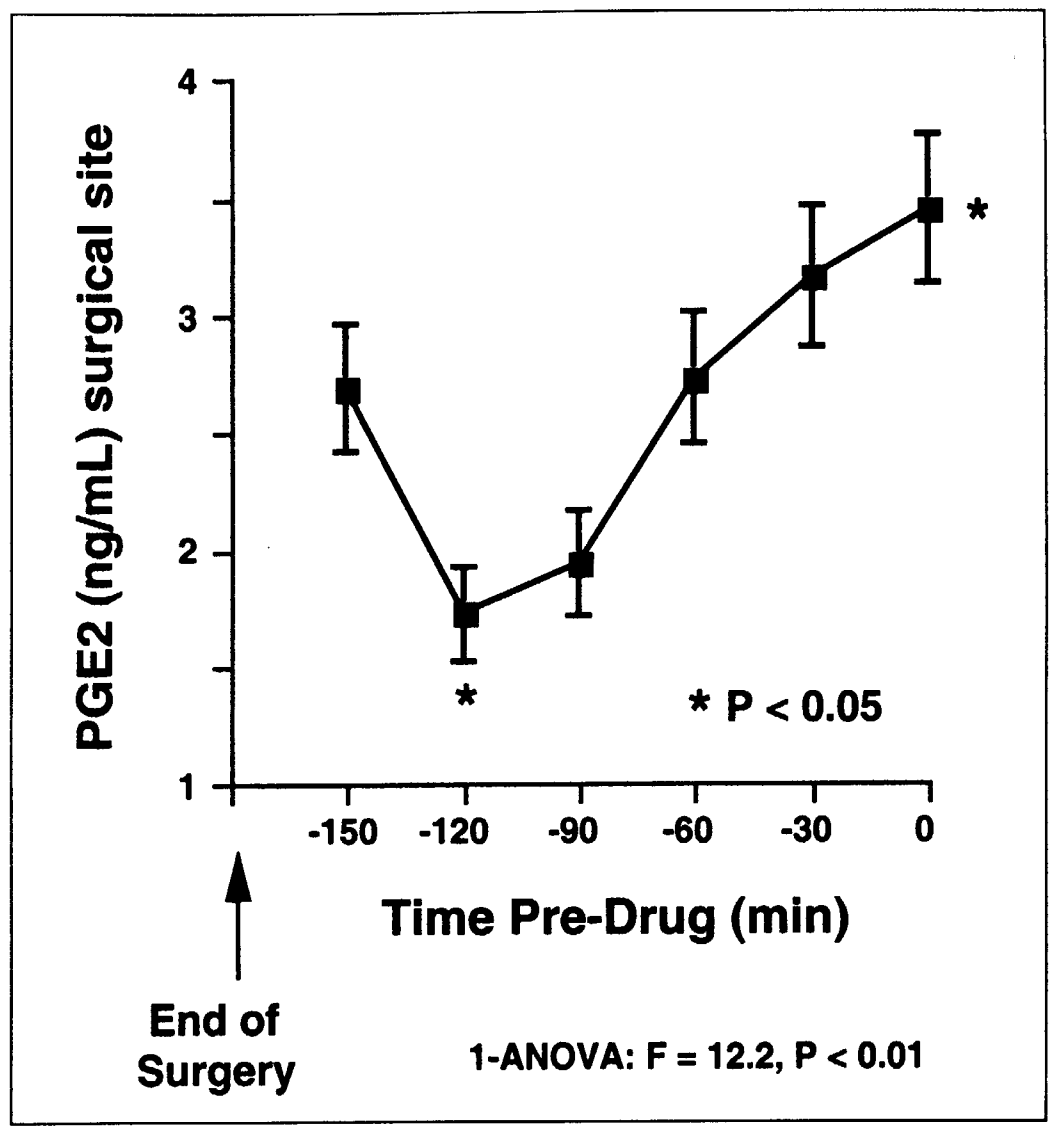

Figure 3. Mean levels of prostaglandin E_2 following oral surgery as collected by a microdialysis probe placed under the mucoperiosteal flap. A significant decrease was demonstrated from the first sample collected immediately post-operatively; PGE_2 increased significantly at the last sample prior to analgesic administration. Adapted from Dionne *et al.*, 1996.

surgery model could not differentiate between pre- and post-operative administration (Sisk and Grover, 1990), suggesting that pre-operative administration is not critical for suppressing pain onset. Recognition of the induction of cyclo-oxygenase (COX)-2 in the post-operative period (Seibert *et al.*, 1994) suggests that blockade of the formation of prostanoids released during surgery by constitutive COX-1 is less important than suppression of COX-2 and prostanoid release during the post-operative period. This is supported by observations (Fig. 3) that levels of prostaglandin E_2 in the first immediate post-operative sample (presumably reflective of surgical trauma) collected from the extraction site by microdialysis are detectable, decrease over the first 60 min post-operatively, and then start to increase over the next 60 to 120 min coincident with the onset of post-operative pain (Dionne *et al.*, 1996). Consistent with this observation is the demonstration that both pre-operative and post-operative administration of 800 mg ibuprofen suppresses pain and prostaglandin E_2 levels at the extraction site (Roszkowski *et al.*, 1997). These observations support the administration of ibuprofen and other NSAIDs prior to the induction of COX-2 and subsequent release of prostanoids as a preventive analgesic strategy for suppressing pain in the immediate post-operative period as well as to inhibit peripheral and central hyperalgesia that produces pain at later time points.

(IV) Analgesic Activity of Ibuprofen Isomers

The biological actions of NSAIDs often reside partly or exclusively in one of the enantiomers (Ariens, 1983). When 2-aryl-

propionic acids, such as ibuprofen, are tested for cyclo-oxygenase inhibition *in vitro*, the activity resides almost exclusively in the S(+) isomer (Caldwell *et al.*, 1988). Ibuprofen is synthesized and administered clinically as a racemic mixture of the S(+) and R(-) isomers; a unidirectional conversion of the inactive R(-) isomer to the pharmacologically active S(+) isomer results in metabolic activation of the racemic drug (Lee *et al.*, 1985). When given in equal amounts of the S(+) isomer, *i.e.*, 400 mg racemic ibuprofen *vs.* 200 mg of the S(+) isomer, both drugs should be essentially the same. The racemic mixture may even have a slightly longer duration of action due to conversion of the R(-) isomer to the S(+) isomer over time. Conversely, conversion of racemic ibuprofen to the active S(+) isomer may contribute to variability in analgesia across individuals and may explain the poor relationship observed between plasma concentrations of ibuprofen and clinical response for acute pain (Laska *et al.*, 1986) and rheumatoid arthritis (Grennan *et al.*, 1983).

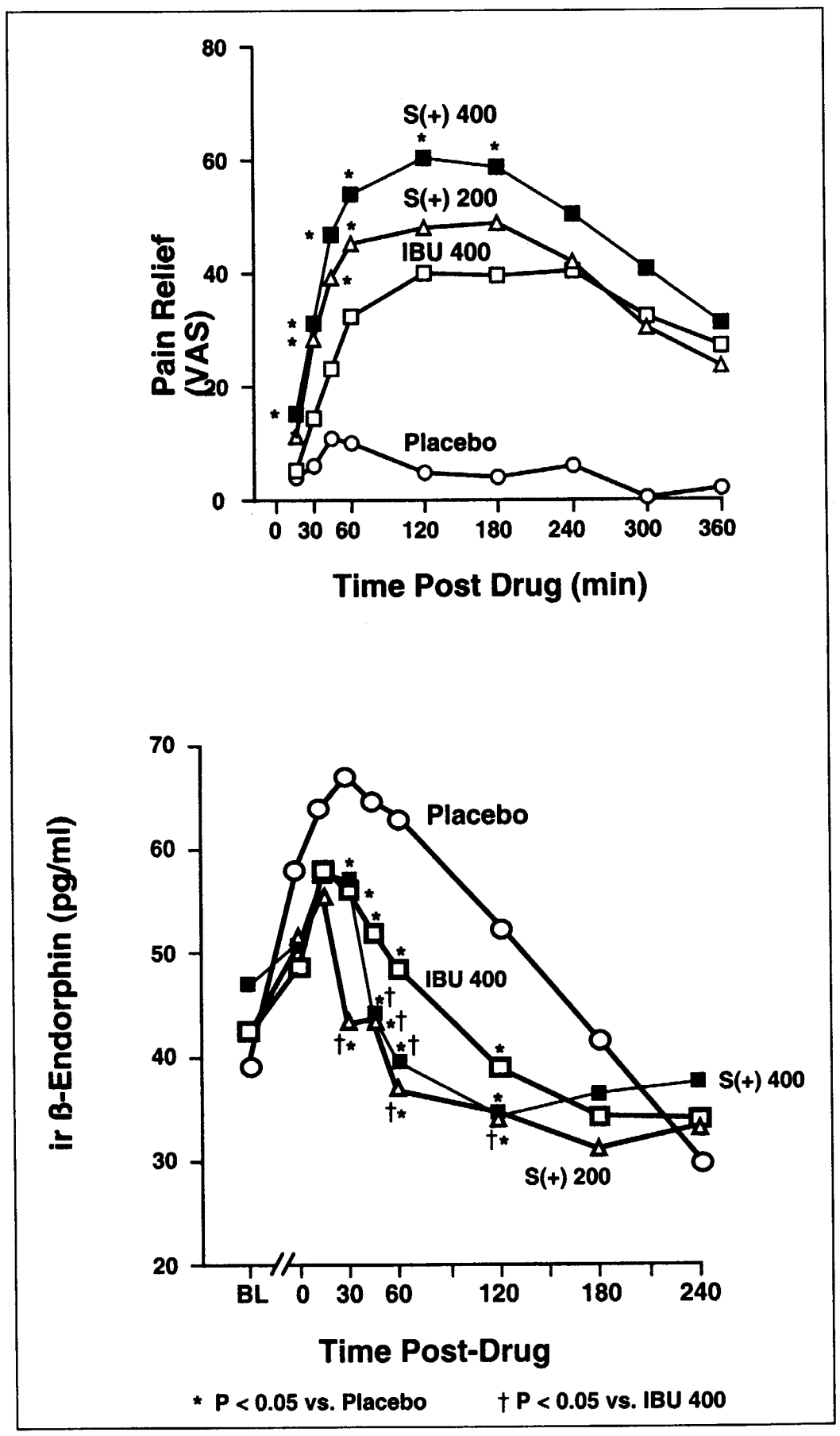

Figure 4. Greater analgesia following administration of the S(+) isomer of ibuprofen in comparison with racemic ibuprofen (upper panel); signficant suppression of plasma β-endorphin temporally associated with decreased pain report (lower panel). Adapted from Dionne and McCullagh, 1998.

The analgesic efficacy of 200 and 400 mg of the S(+) isomer of ibuprofen was compared with that of 400 mg of racemic ibuprofen and placebo for post-operative pain in the oral surgery model (Dionne and McCullagh, 1998). Analgesia was detectable by 15 min for both doses of S(+) ibuprofen in comparison with placebo and was significantly better than that of either placebo or racemic ibuprofen over the first 60 min, with the 400-mg dose of the S(+) isomer producing greater analgesia than racemic ibuprofen up to 180 min post-drug administration (Fig. 4, upper panel). Total pain relief over the six-hour observation period was greater for the 400-mg dose of S(+) isomer in comparison with that of both placebo and the 400-mg racemic dose. Onset of analgesic activity, as measured by patients' subjective report, was significantly faster for both doses of the S(+) isomer in comparison with the racemic formulation. Despite these encouraging findings, confirmatory studies are needed to determine if the advantage for the S(+) isomer was due to the greater intrinsic activity of the isomer or a difference between the racemic formulation and the S(+) ibuprofen formulation.

The existence of two enantiomers of ibuprofen suggests that any delay in onset associated with the administration of racemic ibuprofen is due to the delay in hepatic conversion of the inactive R(-) form to produce therapeutic levels of the active S(+) isomer (Geisslinger *et al.*, 1990). Similarly, the peak analgesic effect of racemic ibuprofen may be limited by the concentration of the S(+) isomer achieved by the balance between the amount administered in the racemic mixture, incomplete conversion of the R(-) isomer to the S(+) isomer (Lee *et al.*, 1985; Geisslinger *et al.*, 1990), and faster renal elimination of the R(-) isomer than for the S(+) isomer (Ahn *et al.*, 1991). Inter-individual differences in the therapeutic response to racemic ibuprofen may be related to variability in the pharmacokinetic activation of the active isomer of ibuprofen.

(V) NSAID-containing Combinations and Formulations

(A) Ibuprofen plus codeine

While ibuprofen and related NSAIDs have proved to be very effective for dental pain, the fact that analgesia cannot be enhanced simply by increasing the dose has led to attempts at additive analgesia by combining ibuprofen with orally effective opioids, a re-invention of the classic analgesic combination. Results, however, have been generally disappointing. Cooper *et al.* (1982) evaluated the combination of a single dose of 400 mg ibuprofen plus 60 mg codeine in comparison with each drug alone, placebo, and the combination of aspirin 650 mg plus codeine 60 mg. While the ibuprofen-plus-codeine combination resulted in slightly higher mean hourly analgesic scores and produced substantially greater analgesia than codeine 60 mg, the combination did not produce significantly greater analgesia than ibuprofen 400 mg alone (Fig. 5). Comparison of ibuprofen 400 mg plus codeine 60 mg with ibuprofen 400 mg in another study demonstrated significant differences in several, but not all, derived measures of analgesic activity (Petersen *et al.*, 1993). Side-effects were more frequent following the opioid-containing com-

bination but consisted of minor adverse events such as drowsiness and "faintness". McQuay *et al.* (1989) demonstrated a 30% increase in analgesic effect with the addition of 20 mg codeine to 400 mg ibuprofen in a crossover study that evaluated two doses of the drugs. With the 20-mg dose of codeine, no tendency for greater incidence of adverse effects was detected, and greater than 70% of subjects expressed a preference for the combination.

These and other similar studies provide a basis for adding codeine to a 400-mg dose of ibuprofen to produce additive analgesia but will likely produce a dose-related increase in side-effects. The minimum dose of codeine needed for additive analgesic activity and the dose which produces unacceptable side-effect liability are not clear. An additive analgesic effect for a 15-mg dose of codeine in combination with ibuprofen 200 mg could not be demonstrated with a sample size (N = 36 or 37 *per* group) usually sufficient to separate treatments in the oral surgery model (Giles *et al.*, 1986). The combination of 20 mg codeine and a 300 mg sustained-release formulation of ibuprofen also did not produce additive analgesia in comparison with the ibuprofen formulation alone (Walton and Rood, 1990). The duration of the observation period following drug administration (11 hrs) exceeds the expected duration of oral codeine (2 to 3 hrs) such that it is unlikely that any transient advantage due to codeine would be reflected in summary measures of analgesic activity. A comparison of three dose formulations of ibuprofen plus codeine suggests that a 30-mg dose of codeine in combination with 400 mg ibuprofen produced an optimal balance between additive analgesia and side-effects (Frame *et al.*, 1986). The relationship between additive analgesic activity and increasing codeine dose was confounded by the increasing dose of ibuprofen, *i.e.*, 15 mg codeine plus 200 mg ibuprofen, 30 mg codeine plus 400 mg ibuprofen, or 60 mg codeine plus 800 mg ibuprofen, such that the contribution of codeine cannot be reliably assessed with this design. The combination of ibuprofen 400 mg plus codeine 60 mg was also compared with a similar combination containing 30 mg of codeine without a clear separation of the two combinations from each other in terms of analgesic activity or side-effect liability (Giles and Pickvance, 1985).

While equivocal, analysis of these data suggests that a minimum dose of 20 to 30 mg of codeine is needed in combination with 400 mg ibuprofen to produce detectable additive analgesia with minimal side-effects. Administration of a traditional dose of 60 mg codeine will usually produce additive analgesia, but for a relatively short duration (1 to 2 hrs) while producing a significant increase in the incidence of side-effects. In the absence of a fixed dose combination, it may be more practical to initiate analgesic treatment with 400 to 600 mg ibuprofen on a fixed schedule and dispense 30-mg tablets of codeine to be taken as needed for pain not adequately controlled by the NSAID. This strategy will result in exposure to the side-effect liability of the opioid for only those patients in need of additional pain relief, thus resulting in a more favorable therapeutic ratio than exposing all patients to opioids' side-effects even if the additional analgesia is not clinically needed.

(B) Ibuprofen plus oxycodone

Analgesic combinations containing oxycodone (Percocet, Percodan, Tylox) have generally been perceived as more effective than codeine-containing combinations. This appears logical on the basis of the 10- to 12-fold greater oral potency attributed to oxycodone in comparison with codeine (Beaver *et al.*, 1978) but is questionable if the recommended dose of oxycodone in these combinations, 5 mg every 6 hrs, is admin-

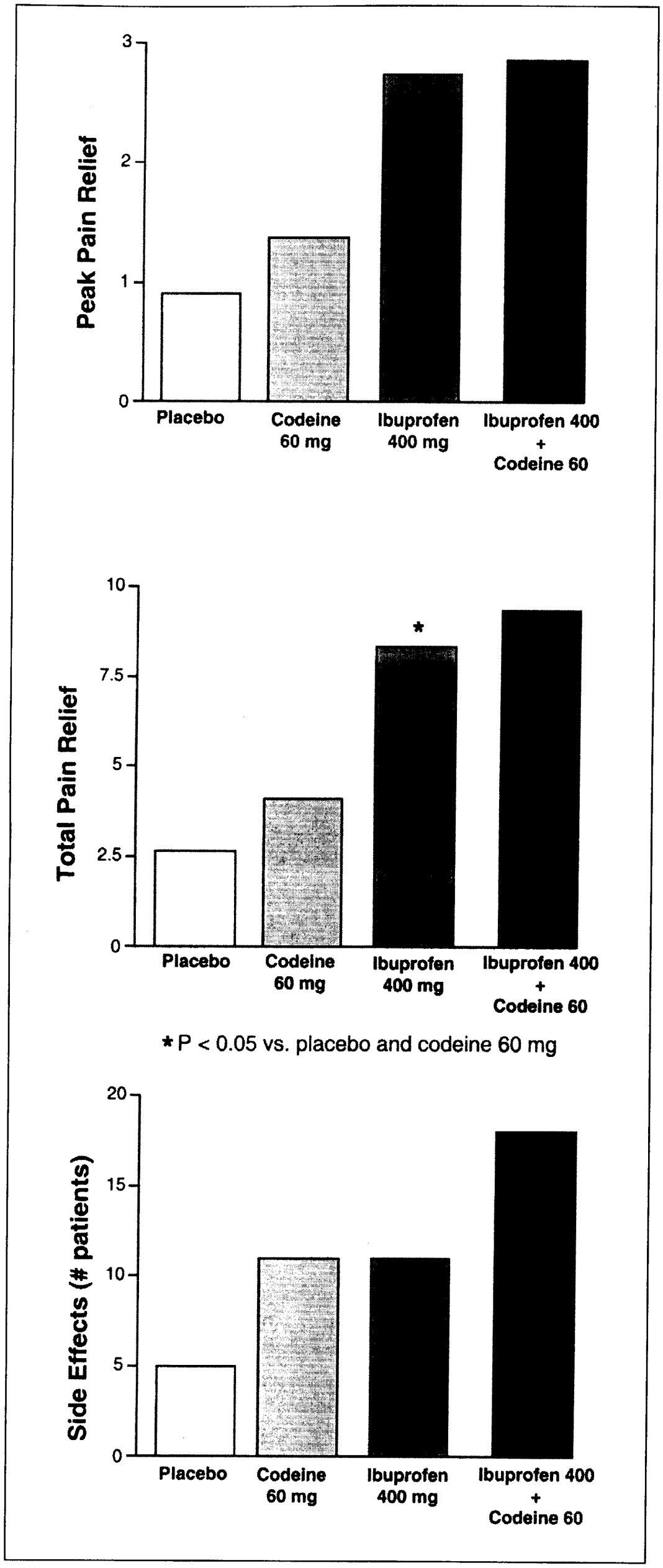

Figure 5. Lack of additive peak analgesic efficacy for 60 mg of codeine in combination with ibuprofen 400 (upper panel) or total pain relief (middle panel) but with an increased incidence of side-effects attributable to the codeine (lower panel). Adapted from Cooper *et al.*, 1982.

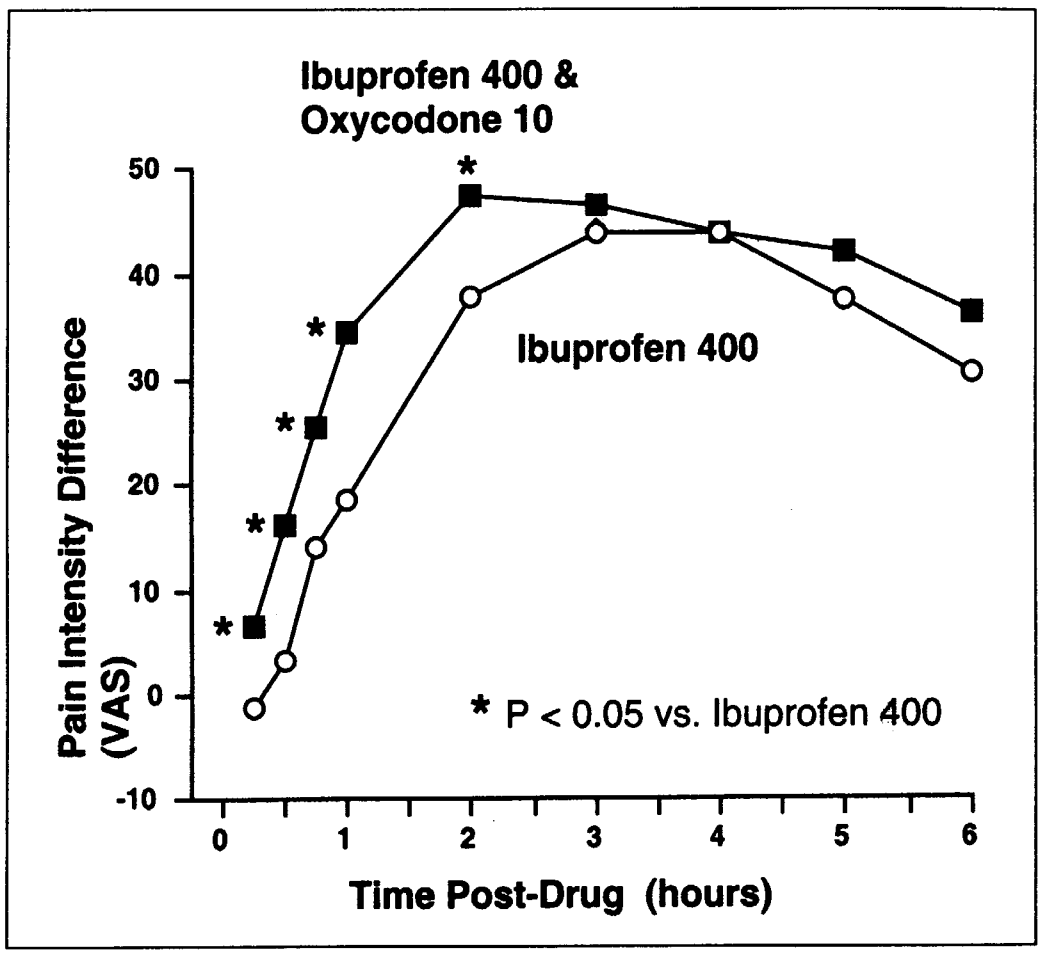

Figure 6. Additive effect of oxycodone 10 mg in combination with ibuprofen 400 at early time points only. Adapted from Dionne, 1999.

istered. This should result in the same analgesia as 50 to 60 mg of codeine, the dose usually administered in combination with aspirin or acetaminophen. Administration of two tablets of a fixed-dose combination containing 5 mg oxycodone should result in a greater analgesia but has been demonstrated to result in adverse effects in approximately 64% of subjects receiving an oxycodone-acetaminophen combination following oral surgery (Cooper *et al.*, 1980).

A dose-response evaluation of 2.5, 5, and 10 mg of oxycodone in combination with 400 mg ibuprofen failed to demonstrate any additive effects for the two lower oxycodone doses (Dionne, 1999). The 10-mg oxycodone dose produced greater analgesia but only over the initial 2 hrs of the study, *i.e.*, until ibuprofen reached its peak effect (Fig. 6). The addition of oxycodone was accompanied by a dose-related increase in side-effects with only five of 30 subjects at the 10-mg dose level not reporting a complaint. Conversely, Cooper *et al.* (1993) found a significant effect for 5 mg oxycodone plus 400 mg ibuprofen in comparison with ibuprofen alone for pain relief at later time points (4 to 6 hrs post-drug) but also with a higher incidence of side-effects than with ibuprofen alone.

The sparse data for oxycodone plus ibuprofen in the oral surgery model limit generalization regarding the potential utility of such a combination in dentistry. Administration of 5 mg oxycodone may produce additive analgesia, probably no greater than that seen for 60 mg codeine, while resulting in the usual opioid side-effects in ambulatory patients: drowsiness, nausea, and vomiting. Increasing the oxycodone dose to 10 mg will likely result in additive analgesia but with a marked increase in side-effects. The lack of an ibuprofen-plus-oxycodone combination and the regulatory restrictions placed on oxycodone when prescribed as a single entity make the clinical utility of this combination for use in dentistry questionable.

(C) Ibuprofen plus hydrocodone

The combination of ibuprofen 200 mg plus hydrocodone 7.5 mg is reported to produce an additive effect for post-operative pain (Wideman *et al.*, 1999). However, there are no published studies that have compared the combination of 200 mg ibuprofen plus 7.5 mg hydrocodone with the effects of 400 to 600 mg of ibuprofen alone. Demonstration of superiority for the combination to either 7.5 mg of hydrocodone alone or 200 mg of ibuprofen alone is insufficient evidence that the marketed combination is superior to the effects of over-the-counter NSAIDs (ibuprofen, naproxen, ketoprofen), aspirin, or acetaminophen, or prescription doses of ibuprofen or other NSAIDs. Even if analgesic equivalency were established for the combination in comparison with 400 to 600 mg ibuprofen or its equivalent, it is likely that a greater incidence of CNS and gastrointestinal side-effects would occur in the opioid-containing combination.

The therapeutic advantage for the use of an ibuprofen-hydrocodone combination rests in the addition of a normal therapeutic dose of ibuprofen (from 400 to 600 mg) with a dose of the opioid that produces additive analgesia with a tolerable incidence of side-effects. Combining one tablet of the marketed fixed-dose combination with one or two tablets of non-prescription ibuprofen would result in a combination containing from 400 to 600 mg of ibuprofen and 7.5 mg hydrocodone. Extrapolating from a dose-response comparison of ibuprofen and oxycodone (Dionne, 1999), it is likely that 7.5 mg of hydrocodone would result in a marginal additive analgesic effect in combination with 400 mg of ibuprofen, but with a greater incidence of side-effects than the use of the ibuprofen alone. The use of two tablets of the marketed, fixed-dose formulation (Vicoprofen) in an ambulatory patient population results in additive analgesia that is greater than that of either drug alone (Wideman *et al.*, 1999), but will also likely produce an excessive number of adverse effects in ambulatory dental outpatients. The currently marketed fixed-dose combination of ibuprofen and hydrocodone should be reserved for clinical situations where 400 to 600 mg of ibuprofen provides inadequate pain relief. Patients should be instructed to take one tablet of the combination with one or two tablets of ibuprofen every 4 to 6 hrs, not to exceed the recommended maximum dose of the combination or the recommended daily maximum for ibuprofen (3200 mg *per* 24-hour period).

(D) Ibuprofen formulations

Formulations of ibuprofen have been developed to enhance onset, potentiate analgesia, and extend the duration of action. The lysine salt of ibuprofen demonstrated faster onset, greater peak analgesia, and a longer duration of action than 500 mg of aspirin for moderate to severe dental pain (Nelson *et al.*, 1994). Ibuprofen lysine had a significantly faster onset of action and greater peak analgesia than 1000 mg of acetaminophen in a similar dental pain study (Mehlisch *et al.*, 1995). The lack of a direct comparison in these studies with the usual racemic ibuprofen formulation does not permit any conclusion to be drawn regarding the possible clinical advantage of the lysine salt. Cooper *et al.* (1994) evaluated the relationship between analgesic efficacy and drug levels of the S(+) isomer of ibuprofen lysine (400 mg), 400 mg of racemic ibuprofen lysine, and 400 mg of racemic ibuprofen in the oral surgery model. At 30 min post-drug, both S(+) ibuprofen lysine and racemic ibuprofen lysine resulted in significantly greater pain relief than racemic ibuprofen. The lysine salts both resulted in greater peak analgesia and total analgesic scores over the first 3 hrs in comparison with racemic ibuprofen. This latter study suggests that the lysine salt of ibuprofen may enhance the onset of analgesia normally seen

following administration of racemic ibuprofen, yet produce greater peak analgesia and comparable duration of action. Formulation differences between the two preparations may explain the apparent analgesic advantage, but caution is needed in the absence of further confirmatory data.

Ibuprofen has been evaluated in the dental pain model in combination with caffeine to potentiate the effects of low ibuprofen doses (from 100 to 200 mg). A combination of 200 mg ibuprofen plus 100 mg of caffeine enhanced the analgesic effect of 200 mg ibuprofen and resulted in analgesia comparable with that of 400 mg of ibuprofen (McQuay *et al.*, 1996) but without any increased frequency of side-effects. A relative potency comparison of ibuprofen alone with ibuprofen in combination with 100 mg caffeine demonstrated a two- to three-fold potentiation of analgesic efficacy over this dose range (Forbes *et al.*, 1991). While demonstration of caffeine's potentiation of ibuprofen analgesic activity may be useful for extrapolation to the use of ibuprofen as a non-prescription analgesic for mild pain, the advantage of this combination for dental pain is not clear. Administration of the usual therapeutic dose of 400 mg of ibuprofen should result in similar analgesia and less side-effect liability.

A controlled-release formulation of ibuprofen which releases 200 mg of drug immediately, followed by release of the remaining drug over 12 hrs, has been evaluated in the oral surgery model. Cooper *et al.* (1993) demonstrated that controlled-release ibuprofen had an analgesic onset comparable with that of ibuprofen, a higher peak effect, and was significantly more effective 4 hrs after administration than was 200 mg of ibuprofen alone. Similar overall effects were reported in a similar study, with the ibuprofen controlled-release formulation providing greater analgesia at 3, 4, and 5 hrs post-drug than 3 doses of 200 mg ibuprofen every 4 hrs (Desjardins *et al.*, 1991). Analysis of these data indicates that the controlled-release formulation of ibuprofen is effective for long-acting analgesia without the therapeutic variability associated with the offset of one dose and onset of the next dose. The effective dose of ibuprofen in this formulation, 200 mg over 4 hrs, is below the normal therapeutic range of ibuprofen for dental pain—from 400 to 600 mg every 4 hrs. While the demonstration of sustained efficacy could be extrapolated to other therapeutic uses of ibuprofen, comparison with repeated doses of 400 to 600 mg are needed to determine if a controlled-release formulation provides analgesia comparable with that of by-the-clock administration of the usual ibuprofen dose for moderate to severe pain.

(VI) COX-2 Inhibitors

Research into the pathophysiology of inflammatory pain led to recognition that there are at least two forms of the cyclo-oxygenase enzyme responsible for the formation of products of the arachidonic acid cascade. One form, characterized as COX-1, is responsible for the normal homeostatic functions of prostaglandins in the gastrointestinal tract that maintain GI mucosa integrity, initiate platelet aggregation, and regulate renal blood flow. The other form, COX-2, was initially thought to be induced only during inflammation and to contribute to the pain, edema, and tissue destruction associated with acute inflammation, rheumatoid arthritis, and osteoarthritis. It is now recognized that the COX-2 enzyme is also expressed in the brain and kidneys and plays an as-yet-undefined physiologic role in these tissues.

The NSAIDs' spectrum of activity reflects their generally accepted mechanism, which is to suppress the activity of both the COX-1 and COX-2 isoforms of cyclo-oxygenase, with a resultant decrease in the production of arachidonic acid cascade metabolites. Observations that COX-1 is constitutively distributed throughout the body, while COX-2 expression is limited to a few specialized tissues and is induced during inflammation, led to the hypothesis that COX-1 is primarily responsible for the adverse gastrointestinal effects of existing dual COX-1/COX-2 inhibitors, while COX-2 mediates the synthesis of prostanoids during pathological processes. This hypothesis suggests that dual COX-1/COX-2 inhibitors such as ibuprofen produce both therapeutic and toxic effects at therapeutic doses, while selective COX-2 inhibitors should have therapeutic effects largely devoid of NSAID toxicity.

Two drugs now entering the market are highly selective for COX-2 suppression at the doses administered clinically, with minimal effects on COX-1 activity. The specificity of rofecoxib for COX-2 *vs.* COX-1 inhibition was demonstrated in males administered doses up to 375 mg daily for 14 days (Van Hecken *et al.*, 1999). There was a significant, dose-related inhibition of prostaglandin E_2 ($PGE_{2)}$ without inhibiton of thromboxane formation, thereby providing evidence that rofecoxib is a selective inhibitor of COX-2 in humans without evidence of COX-1 inhibition in doses eight-fold higher than doses associated with clinical analgesic efficacy. The expectation is that they will provide therapeutic efficacy comparable with that of current NSAIDs, but without the gastrointestinal and renal toxicity which contributes directly to the morbidity and mortality associated with chronic NSAID administration.

Single doses of celecoxib were demonstrated, in the oral surgery model of acute pain, to be superior to placebo (at all doses reported in published abstracts), comparable with that of 650 mg of aspirin, but generally less effective than standard doses of naproxen. In multiple-dose studies conducted in patients following orthopedic and general surgery, celecoxib's analgesic efficacy was inconclusive. As a consequence of these data, celecoxib did not receive approval for the management of acute pain, since it fails to satisfy the criteria of demonstrating analgesic efficacy in at least two different pain models. Celecoxib was more effective than placebo for the treatment of osteoarthritis and was approved and marketed for that indication.

Rofecoxib appears to have greater analgesic efficacy than

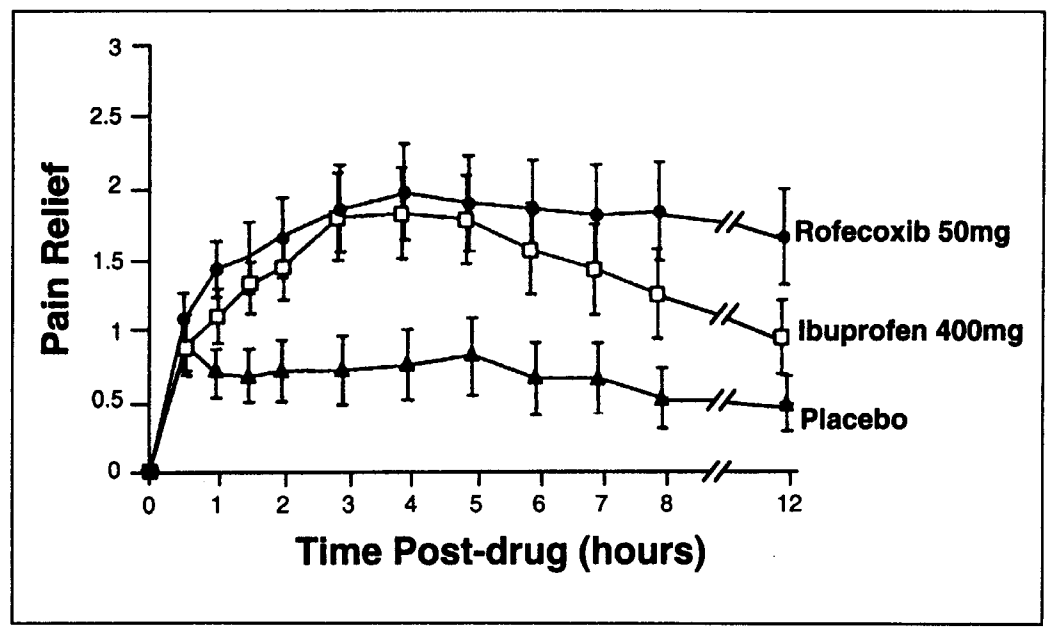

Figure 7. Comparison of the analgesic effects of the COX-2 inhibitor rofecoxib in comparison with ibuprofen 400 mg and placebo. Adapted from Brown *et al.*, 1999a.

celecoxib, based on the results of studies in the oral surgery model and in patients with painful dysmenorrhea. Rofecoxib was compared with ibuprofen 400 mg and placebo in a single-dose study in the oral surgery model of acute pain, with traditional analgesic endpoints as well as the two-stopwatch method for estimating analgesic onset (Fig. 7). The total pain relief and sum of the pain intensity difference score over 8 hrs following a single 50-mg dose of rofecoxib were superior to those of placebo but not distinguishable from those of ibuprofen 400 mg (Brown *et al.*, 1999a), arguably the maximal ibuprofen dose for acute pain. The median time to onset of pain relief was indistinguishable for rofecoxib (0.7 hr) and ibuprofen (0.8 hr), but significantly fewer subjects in the rofecoxib group required additional analgesic within 24 hrs as compared with the placebo or ibuprofen groups. In a second study comparing rofecoxib in doses of 12.5, 25, and 50 mg with naproxen 550 mg and placebo, a clear dose response was demonstrated for analgesia (Fricke *et al.*, 1999). The 25- and 50-mg doses of rofecoxib were numerically superior but statistically indistinguishable from naproxen for both pain relief and pain intensity difference. In both studies, the incidences of clinical and laboratory adverse experiences were similar.

Rofecoxib's analgesic efficacy was also evaluated in replicate studies for primary dysmenorrhea, generally accepted as a sensitive model of acute pain. Subjects with a self-reported history of moderate to severe dysmenorrhea received rofecoxib 50 mg, naproxen 550 mg, or placebo in a cross-over study over three menstrual cycles (Brown *et al.*, 1999b). Both rofecoxib and naproxen produced greater analgesia over 8 hrs as assessed by pain relief and pain intensity difference scores, time to onset of pain relief, and percent of patients requiring additional analgesic over the first 12 hrs. In a similar study, 25 and 50 mg rofecoxib and naproxen 550 mg were superior to placebo but indistinguishable from each other on all measures of efficacy (Daniels *et al.*, 1999). In both of the dysmenorrhea studies, the incidences of clinical and laboratory experiences were reported as similar across groups.

Both celecoxib and rofecoxib appear to have reduced risk for producing gastrointestinal perforations, ulcers, and bleeding than traditional NSAIDs such as ibuprofen, diclofenac, and indomethacin, based on data presented to the FDA Arthritis Advisory Committee. But concern was raised as to whether the standard NSAID warnings regarding gastrointestinal and renal toxicity should also be extended to new COX-2 selective inhibitors until greater experience has been gained with these new molecular entities. Recent reports of fatal gastrointestinal hemorrhage in 10 patients who were taking celebrex are inconclusive epidemiologic evidence but emphasize the prudence of waiting until greater clinical experience has been gained with this drug before concluding that it has a more favorable gastrointestinal safety profile than standard NSAIDs.

A recent study reported that 10 days' administration of rofecoxib had no effect on the anti-platelet activity of low-dose aspirin (81 mg once daily) as measured by serum thromboxane B2 activity and platelet aggregation (Greenberg *et al.*, 1999). This suggests that the drug could be safely administered to patients who are taking prophylactic aspirin to reduce their potential for cardiovascular disease. An evaluation of the influence of antacids on the bioavailability of rofecoxib did not detect any significant effect on plasma concentrations of the COX-2 inhibitor, suggesting that co-administration of these two drug classes should not have any adverse effect on clinical activity (Schwartz *et al.*, 1999).

Limited data assessing the efficacy and safety of the new COX-2 inhibitors have been presented, mostly in abstract form, at professional meetings and to the FDA Advisory Panels considering the New Drug Applications of each drug, so that proprietary information will not be divulged. Now that both drugs have been approved, it is hoped that much of this information will appear in the scientific and clinical literature, to facilitate better assessment and dissemination of the balance between efficacy and safety. In light of the modest analgesic activity demonstrated for celecoxib (Celebrex), its failure to be approved for an acute pain indication, and disturbing early reports to the FDA of fatal gastrointestinal bleeding, dentists should avoid using this drug until more clinical experience has been gained and new studies conducted demonstrating clear evidence of analgesic activity in the oral surgery model.

The data published in abstract form for rofecoxib provide clear evidence of an acute analgesic effect in replicate studies in two models of acute pain and selectivity for COX-2 inhibition. The drug is well-tolerated following single doses and does not appear to inhibit COX-1-mediated platelet aggregation. These data provided a basis for approval of rofecoxib, in the US, as the first selective COX-2 inhibitor indicated for the management of acute pain (up to a maximum of 5 days) as well as for the treatment of osteoarthritis. The analgesic activity for a 50-mg dose of rofecoxib should be comparable with that of 400 mg ibuprofen, its expected gastrointestinal safety is predicted to be less than that of dual COX-1/COX-2 inhibitors like ibuprofen, but its effects on the kidney with widespread administration are yet to be determined.

Most dental outpatients are adequately managed on nonprescription doses of NSAIDs at a nominal cost to the patient. Pain following dental procedures, even the removal of impacted third molars, is transient over the first 1 to 3 days following the procedure and usually does not require analgesic treatment beyond what is achieved with NSAIDs. In addition, patients have usually been previously exposed to aspirin, acetaminophen, or over-the-counter formulations of ibuprofen, making it unlikely that they will experience an idiosyncratic or allergic response when given one of these drugs following a dental procedure. These considerations suggest that while the new selective COX-2 inhibitor, rofecoxib, holds promise for analgesic efficacy with greater safety than ibuprofen and related NSAIDs, it would be prudent to wait until additional clinical experience in patients with osteoarthritis documents this predicted safety.

(VII) Effects on Edema

The acute post-operative sequelae of dental procedures includes other signs of inflammation due to tissue injury, most prominently edema. While synthetic analogs of endogenous corticosteroids are used extensively to control the sequelae of both acute and chronic inflammation, their use post-operatively is tempered by their ability to suppress the immune system, thereby increasing the risk of infection. NSAIDs have a more selective mechanism of action than glucocorticoids and a more favorable side-effect profile, suggesting that drugs of this class may inhibit inflammation without the risks of corticosteroid administration. Ibuprofen produced a trend for reduced swelling in comparison with placebo when given for three days at a dose of 400 mg three times daily (Lokken *et al.*,

1975). Administration of 600 mg ibuprofen four times a day for two days also showed a trend toward suppressed edema formation at 48 hrs following oral surgery (Troullos *et al.*, 1990). A retrospective analysis of the data from two studies, done in series, evaluating the effects of two NSAIDs (ibuprofen and flurbiprofen) led to the conclusion that NSAIDs significantly suppress edema formation following oral surgery in comparison with placebo (Troullos *et al.*, 1990). A more recent study concluded that the combination of ibuprofen 400 mg three times *per* day and 32 mg of methylprednisolone reduced swelling by greater than 50% in comparison with placebo (Schultze-Mosgau *et al.*, 1995). The lack of separate groups receiving either ibuprofen alone or methylprednisolone does not permit any conclusion to be drawn about the contribution of ibuprofen to the total effect on reduced swelling.

While somewhat inconclusive, the observations from the two studies, in which ibuprofen was administered alone, demonstrated a reduction in swelling in comparison with placebo, with minimal side-effects and no evidence of interference with healing or peri-operative bleeding.

(VIII) Interactions with Plasma β-endorphin

Pain activates the pituitary-adrenal axis with subsequent pituitary secretion of β-endorphin, leading to elevated circulating β-endorphin levels. Clinical studies in the oral surgery model demonstrate that β-endorphin is released in response to surgical stress in conscious patients (Hargreaves *et al.*, 1986; Troullos *et al.*, 1997) and during post-operative pain (Hargreaves *et al.*, 1986, 1987a,b). Plasma β-endorphin levels are also elevated during surgery performed under general anesthesia but remain stable if regional or spinal anesthesia is administered prior to surgery, demonstrating that peripheral nociceptive input activates supra-spinal sites, leading to pituitary β-endorphin secretion even in unconscious patients not perceiving pain (Janicki *et al.*, 1993; Gordon *et al.*, 1997a,b). These observations suggest that increased β-endorphin is an index of nociceptive input into the central nervous system.

Ibuprofen affects the release of β-endorphin during both surgical stress and post-operative pain. Administration of ibuprofen 600 mg before oral surgery results in increased release of β-endorphin intra-operatively, in comparison with the elevated levels seen during surgery in a placebo group. Parallel *in vivo* and *in vitro* studies indicate that ibuprofen potentiation of endorphin release is mediated at the level of the pituitary corticotroph cell, possibly by interfering with ultrashort feedback inhibition modulated by prostaglandins (Troullos *et al.*, 1997). The time course of this enhanced release seems to coincide with the duration of surgery such that β-endorphin levels decrease in samples collected after surgery and return to baseline within 60 min after the completion of surgery. The use of local anesthetic should largely block the perception of pain during surgery, and any residual unpleasant sensations would be similar in the placebo group. Thus, the interaction demonstrated between ibuprofen and elevated β-endorphin levels during surgery can likely be attributed to potentiation of stress-induced release of β-endorphin.

Administration of the S(+) isomer of ibuprofen following pain onset in the oral surgery model results in a decrease in plasma β-endorphin levels (Dionne and McCullagh, 1998) coincident with a reduction in pain. Levels were also reduced to a lesser extent in a parallel group receiving racemic ibuprofen, consistent with the lower levels of the S(+) isomer in the racemic ibuprofen group, in comparison with the group receiving the pure S(+) isomer. These observations suggest that ibuprofen administration in patients reporting acute pain suppresses pituitary β-endorphin release coincident with analgesia, presumably by decreasing nociceptive activation of the pituitary-adrenal axis.

(IX) Use for Chronic Temporomandibular Pain

Pharmacologic intervention in the management of chronic orofacial pain is usually considered adjunctive to definitive treatment, based on the assumption that more definitive treatments will eventually correct the underlying pathophysiologic process. It is now recognized that many putative dental and surgical therapies for temporomandibular disorders (TMD) have not withstood scientific scrutiny. This has led to the use of drugs as the primary intervention for some forms of chronic orofacial pain. Palliative management of intractable pain may also be considered as an indication for pharmacologic management when pain is poorly controlled following failed treatments, such as surgical interventions or when no other treatment is available. While the use of analgesics for acute orofacial pain is well-documented through hundreds of controlled clinical trials, the use of a broad spectrum of drugs for chronic pain is based on very few studies. Even in the absence of a therapeutic benefit, however, toxicity associated with chronic administration of the drug can still occur. Recognition of the chronic adverse renal and gastrointestinal effects of NSAIDs indicates a need for critical examination of their use for chronic pain conditions such as TMD.

A meta-analysis of the literature on TMD published from 1980 to 1992 identified more than 4000 references (Antczak-Bouckoms, 1995), but only 1% (N = 55) were randomized controlled trials. Five of the controlled trials were drug studies, providing an extremely small body of evidence upon which to base generalizations regarding efficacy and toxicity. In addition, many of the studies evaluating pharmacologic treatments are methodologically flawed, with heterogeneous patient samples, lack of an adequate control group, and a failure to use standardized methods for measurement of pain and dysfunction.

A comprehensive review of the primary literature reveals little scientific support for the concept that daily use of NSAIDs offers benefit for chronic orofacial pain (Truelove, 1994). Standard texts (Dworkin *et al.*, 1990) and summaries of expert opinion (American Academy of Orofacial Pain, 1993) often provide recommendations or extrapolate from chronic inflammatory conditions such as arthritis. Yet the results of two placebo-controlled studies suggest that NSAIDs are ineffective for chronic orofacial pain. The analgesic effects of ibuprofen, 2400 mg *per* day for 4 wks, could not be separated from those of placebo in a group of patients with chronic orofacial pain characterized as myogenic in origin (Singer and Dionne, 1997). A similar comparison of piroxicam, 20 mg daily for 12 days, with placebo for TMD pain also failed to demonstrate any therapeutic advantage for the NSAID (Gordon *et al.*, 1990).

Both clinical and animal studies suggest that tolerance to NSAIDs can develop with repeated administration. The mean reduction in chronic lower back pain intensity following an initial dose of 1200 mg ibuprofen was 23% (Walker *et al.*, 1996). After two weeks of 2400 mg *per* day of ibuprofen or placebo, the mean reduction in pain intensity for the last dose was four-fold lower in the drug group. The initial low level of response (23%) suggests that low back pain is not particularly sensitive to

ibuprofen and may explain, in part, the poor response seen for chronic musculoskeletal pain in the orofacial area. The development of tolerance over 2 wks would suggest a similar process for TMD pain which could make the analgesic response negligible by the end of 4 wks. Tolerance to diflunisal, with repeated adminstration, has been demonstrated in animals without a reduction in the amount of drug in the blood over time following administration of the first dose in comparison with a dose given following three days of diflunisal (Walker and Levy, 1990). This suggests a functional change in the pharmacologic response rather than enhanced pharmacokinetic disposition, such that the same amount of drug elicits less analgesia.

The lack of clinical studies to support the efficacy of ibuprofen for TMD is in contrast to the growing body of evidence (for review, see Rainsford, 1998) on the potential serious toxic effects of NSAIDs when given chronically at high doses. A short trial of an NSAID may be considered in patients with an apparent inflammatory component to their pain complaint. A lack of therapeutic effect after a seven- to 10-day trial or the development of any GI symptoms should prompt discontinuation of the NSAID.

(X) NSAIDs as Adjuncts to Periodontal Therapy

There has been considerable interest over the past decade on the use of non-surgical pharmacotherapy for the adjunctive management of periodontal disease. Many studies have evaluated the use of antibiotics to reduce the number of potential periodontal pathogens as an adjunct to traditional periodontal therapy. NSAIDs have also been used to modify the host response to periodontal disease. It is generally recognized that prostaglandins are associated with gingivitis and alveolar bone loss. Metabolites of the arachidonic acid cascade are potent stimulators of bone resorption (Dietrich *et al.*, 1975; Raisz *et al.*, 1979; Dewhirst, 1984; Neuman and Raisz, 1984). NSAIDs have been shown to slow bone loss due to periodontitis significantly in both animal models and clinical evaluations (Williams *et al.*, 1989; Jeffcoat *et al.*, 1995; Puette *et al.*, 1997). Both NSAID ingestion and oral rinses reduce the severity of gingivitis while lowering the gingival crevicular fluid levels of prostaglandin E_2 and leukotriene B_4 levels *via* an inhibition of the cyclo-oxygenase enzyme (Johnson *et al.*, 1990; Heasman *et al.*, 1993). These examples support the hypothesis that by-products of arachidonic acid metabolism play a role in the pathogenesis of gingivitis and alveolar bone loss, and that their inhibition by NSAIDs decreases clinical manifestations of periodontal disease.

Comparison of an NSAID administered systemically (50 mg flurbiprofen b.i.d.) with an NSAID rinse (0.1% ketorolac b.i.d.) for 6 mos indicated that the ketorolac rinse preserved more alveolar bone than the systemic drug administration (Jeffcoat *et al.*, 1995). In another study, ketorolac rinse (0.1% b.i.d.), ketorolac capsules (10 mg b.i.d.), flurbiprofen (50 mg b.i.d.), and placebo rinse and capsule were utilized to examine gingival crevicular levels of PGE_2 and measure alveolar bone loss by digital subtraction radiography (Cavanaugh, 1995). The concentration of ketorolac was greater in the gingival crevicular fluid following the 0.1% oral rinse than with the 10-mg ketorolac capsule. A significant loss of bone height was observed in the placebo group but not with the flurbiprofen tablet or ketorolac oral rinse. This study also demonstrated that the systemic plasma levels of ketorolac rinse were far below that of the 10-mg ketorolac levels of the tablet. These data support ketorolac rinse as an adjunct for long-term therapy for the treatment of adult periodontitis while minimizing the incidence of systemic complications.

(XI) Recommendations for the Use of NSAIDs in Dentistry

NSAIDs are among the most widely used drug classes for dental pain, along with aspirin, acetaminophen, and codeine. They are generally more efficacious than these standard drugs in most studies, presumably due to the inflammatory etiology of most dental pain and the NSAIDs' prominent anti-inflammatory effects. A single dose of 400 to 600 mg of ibuprofen is usually more effective than combinations of aspirin or acetaminophen plus an opioid, usually codeine or oxycodone, and with fewer side-effects—making it preferable for ambulatory patients who generally experience a higher incidence of side-effects following ingestion of an opioid. Ibuprofen and flurbiprofen also exert a modest suppression of swelling following surgical procedures, providing additional therapeutic benefit but without the potential liabilities of steroid administration. These considerations and the vast clinical experience gained over the past 25 years make ibuprofen the drug of choice for dental pain in patients who do not have contraindications for its use.

Limitations to orally administered NSAIDs for dental pain include delayed onset when compared with an injectable opioid, their inability to relieve very severe pain consistently, and an apparent lack of effectiveness when given repeatedly for chronic orofacial pain. The best strategy for minimizing pain onset is administration of an NSAID prior to the induction of COX-2 post-operatively. For patients who do not receive satisfactory relief from an NSAID alone, combining it with an opioid may provide additive analgesia but will also be accompanied by more frequent side-effects. The optimal balance for an individual patient can be best achieved by supplying the patient with an NSAID to be taken by-the-clock and a separate prescription for codeine 30 mg to be taken if needed and titrated between one and two tablets to achieve pain relief with minimal side-effects. Oxycodone can be given in combination with ibuprofen in a similar manner, while a fixed-dose combination of ibuprofen 200 mg and hydrocodone 7.5 mg is problematic unless co-administered with additional ibuprofen.

The use of repeated doses of NSAIDs for chronic orofacial pain should be re-evaluated in light of their apparent lack of efficacy, and their potential for serious gastrointestinal and renal toxicity and tolerance with repeated dosing. Owing to the lack of suitable alternatives, it is likely that the use of ibuprofen and other NSAIDs for this patient population will continue. However, their use should be limited to a short trial and discontinued if signs of gastrointestinal or renal toxicity are noted.

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